

M A L A R I A
Its Treatment and Prophylaxis.
A T H E S I S
for the
M.D. DEGREE
by
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h. 5. 1919 -



Introduction:-

The subject of Malaria is a theme that requires little apologetic, for there is none in the whole category of Tropical Medicine which has been brought so much before both the Medical and the Lay mind. Its importance may be gathered from the fact that it is responsible for more loss to the community, both with regard to race vitality and labour, than any other single disease. The vital statistics of the most Malarious districts in Lower Bengal where the disease is endemic, and exceedingly prevalent, give death returns from Malaria which run as high as 90% of the total mortality. These returns, however, coming largely as they do from the villages of Bengal, must be sifted in order to obtain the true proportion; as the "vital statistician", usually an illiterate villager, finds it convenient to report every kind of illness outside his ken as "fever". Rogers¹, who took the pains to do this in the case of one fever-stricken district - Dinajpur - found that the actual deaths from Malaria were from 20% to 25% of the total annual mortality, although the case mortality is only 5%. These figures shew a rate of mortality exceeded only by the terrible ravages of epidemics of Cholera and Plague, which from time to time extend their devastating influences over parts of India. Ross², in his recent review of the subject, gives ten to fifteen per thousand of the total mortality as the average due to Malaria, all over the Tropics.

But /

But even more significant in its effects is the loss to the community from the point of view of labour. Field labourers are often laid aside for weeks in one season by recurring attacks ; clerks and servants are often unable to fulfil their day's routine ; the birth-rate of the community is seriously affected ; and even the school children, during the worst months of the year, rarely shew an attendance average of more than two-thirds of that for the rest of the year. In this way, it is calculated that the total work of the community is reduced by at least one-third in those regions where this disease is rampant. And yet, largely through the unceasing efforts of patient workers of various nationalities, all this terrible loss has been proved to be to a large extent, preventible, while the possibility of the ultimate extermination of the disease may be no idle dream.

Although, as Rogers¹ says, "the treatment of Malaria may be summed up in the one word, 'Quinine'"; still there are other drugs and methods of treatment which have found a place in this category. And it may be well to review these briefly before proceeding to the main subject of this thesis.

Arsenic forms the mainstay of Bengali Homeopathy, in the treatment of Malaria ; but the very fact that so many of these patients find their way to Dispensaries where Quinine is prescribed, is in itself sufficient proof of the former's inefficiency. The drug has, however, a very conspicuous place in the treatment of the /

the anaemia which accompanies Malaria, and forms an ingredient in most of the effective prescriptions for the enlarged spleen, which results from repeated attacks of the disease.

Methylene Blue was first used in the treatment of acute Malaria by Guttman and Erlich in 1891, and has been recommended by many physicians since that time. Only the B. X. medicinally pure drug should be used, and even its administration is very often followed by strangury and inflammation of the kidney. But by combining each dose with five grains of Pulvis Myristicae (powdered nutmeg), this unfortunate complication may be prevented. According to Manson the drug should be given in doses of two or three grains every three hours until the urine becomes deeply tinged. Thayer³ writes that his own experience confirms that of most observers, that the efficiency of this drug is far below that of Quinine, and the results uncertain. Thomson⁴ has studied its effects upon the crescents, and concludes that as a result of his careful observations this drug, although not so potent in destroying the sexual parasites, is yet more potent in preventing their formation. He recommends combining Methylene Blue with Quinine, especially in these cases where, owing to the idiosyncrasy of the patient, large doses of Quinine cannot be tolerated. Deaderick⁵ considers it a valuable substitute when Quinine is contra-indicated. This drug has, therefore, still a place in the treatment of Malaria, and may be given combined with Quinine, or /

or as a substitute in special cases.

Picric Acid. Surveyor⁶ has recently carried out a series of investigations with this drug, and reports favourably on it. In most of his cases the acid was given by the mouth in doses of twenty grains three times a day ; but in six cases, where difficulty was experienced in taking the medicine orally, hypodermic injections of the Sodium salt were given. Three Cub.cent. of a 4% solution were injected into the muscles, and those proved to be less painful than Quinine injections. As a control, certain cases were treated with Quinine. The results were encouraging, and may be tabulated thus:-

Picric Acid	-	22 cases	86% cured.
Quinine	-	34 cases	73% cured.

These results were most noticeable in crescent infections, but were not so good in Benign Tertian infections.

Corrosive Sublimate was first given by Bacelli⁷ in 1894 in the treatment of the pernicious forms. He used 1-1000 solution in three pints of Normal Saline, and gave it intravenously. Beginning with the equivalent of 1-50 grain, he gradually increased the dose to 1-6 of a grain. But his experiments were not confirmed, and most modern text-books do not even mention it. Two years ago, however, Deppe⁸ treated with Bacelli's solution a case of subtertian Malaria in which the parasite had disappeared from the peripheral blood, but the temperature still rose for a few hours every day. A latent focus of sepsis was suspected, /

suspected, and .01 gramme of Perchloride of Mercury in normal saline solution was injected intravenously. The result was quite satisfactory as far as the temperature was concerned, but the improvement was accompanied by an attack of diarrhoea which lasted for nearly a week, and proved a very serious complication. This would make one chary of repeating the experiment, although perhaps in this case, owing to the idiosyncrasy of the patient, the dose may have been too large.

Among the newer drugs which have been tried with more or less success are Ethyl-hydro-cuprein (or Optochin), Methyl-hydro-cuprein (or Hydroquinine), Salvarsan, Neo-salvarsan, Arsalyt, Hectine and Antimonium Tartrate. The first two of these are synthetic derivatives of Quinine ; the Constitutional formula of this last being Methyl-cuprein.

Ethyl-hydro-cuprein (or Optoch) & Methyl-hydro-cuprein (or Hydroquinine). MacGilchrist², in his recent brilliant researches on Quinine derivatives, has shed a flood of light upon the mutual relations of those drugs, and their relative value as anti-periodics. By using Infusoria to represent the Malarial parasite, and guinea-pigs to represent the human host, he was able to demonstrate on the one hand, the efficacy of each of these drugs as a parasiticide, and, on the other, their relative lethal power with regard to the human host. It was found that the essential anti-malarial agent was a derivative of piperidine, a fission produce of piperine, which, in

its turn is an alkaloid of *Piper Nigrum* (black pepper); and in this connection it is interesting to note that black pepper used to form an ingredient in some of the anti-periodic preparations employed before the virtues of Quinine were so well known. The results of MacGilchrist's work may be summarised as follows:- Ethyl-hydro-cuprein and Methyl-hydro-cuprein are less lethal to guinea pigs than any of the other *Cinchona* derivatives. Ethyl-hydro-cuprein is more lethal towards infusoria than any of the other Cinchona derivatives; while Methyl-hydro-cuprein is for all practical purposes equal to Quinine, in its lethal power over infusoria.

These results have since been tested clinically in the case of Ethyl-hydro-cuprein, by Izar and ¹⁰ Nicosia, who gave one gramme to 1-5 grm. doses daily intramuscularly in 49 cases of Tertian and Subtertian infections which had resisted Quinine, and found that the symptoms yielded readily, and no relapses occurred. It was very constant in its action, which suggests an affinity for the parasites in all stages of their development.

¹¹ Peiper found as a result of his experience of nineteen cases of Tertian and Subtertian infections, that Methyl-hydro-cuprein is as efficient as Quinine in the Subtertian, and slightly more efficient in the Benign infections.

¹² Baermann administered Methyl-hydro-cuprein intramuscularly in .5 grm. doses with very good results. /

results. Four doses cleared the blood and only four cases out of twelve relapsed. Local reaction was intense. Intravenously he found results were not so trustworthy.

Salvarsan and Neo-Salvarsan. When one considers the good effects obtained by these drugs in spirochaetosis, it was only to be expected that the attempt to "sterilize" the system as regards the Malarial plasmodia should also be made. Catter¹³ relates his personal experience. He suffered from a severe infection of Malaria in 1912. For nearly a year he subjected himself to Quinine treatment, without avail ; but one injection of Neo-salvarsan apparently freed the system of plasmodia, and gave him much general benefit. Ayres¹⁴ reports a case of chronic Malaria cured after two injections of .9 gramme of Neo-salvarsan. Sheard¹⁵ cured a case of Benign Tertian with one injection of the same dose, given shortly before the next rise of temperature was expected. No subsequent rise in temperature occurred, and the parasites disappeared from the peripheral blood. Bactge¹⁶ records four cases of Benign Tertian treated with Neo-salvarsan, there were no further relapses while the cases remained under observation. In the other varieties of Malaria such good results have not been obtained. Werner¹⁷ using Salvarsan, found he could clear the peripheral blood of parasites in 17 hours, whereas with Quinine 36 hours were required. He has tried a combination of Neo-salvarsan and Quinine by injection, and found that a dose of less than /

than half a gramme was now sufficient to effect a speedy cure.

Arsalyt a derivative of Salvarsan, has been given intramuscularly in .5 gramme doses, by Muhlens and Gelhaar¹⁸: One injection was sufficient to cut short the attack, but did not prevent relapses.

Hectine the sodium salt of Benzo-sulpho-p-amino-phenylarsonate has been used by Fontoynt & Razafimpanilo¹⁹, and was found to give good results in those cases where Quinine was contra-indicated, or, better still, in association with it. It is administered in from ten to twenty centi-gramme doses. The histories of eight patients so treated by intramuscular injection shew that it may be given in all cases, except in pernicious attacks where a rapid action is required, and here Quinine is the superior drug. In cases of severe Malaria with leucopaenia, Hectine will succeed where Quinine has failed. It is advisable to give three or four injections of Hectine, then to continue with Quinine injections, and finally to complete the treatment by Hectine. When used alone the results are apt to be uncertain, especially in the case of children. Crespin²⁰ states that in febrile attacks which follow indigestion or fatigue, and in these where crescents are found in the blood, Hectine proves its value. It is an anti-haemolytic, and may thus be used with impunity in cases complicated with "Blackwater fever." He uses it both by injection and by the mouth, and finds that it increases both the red cells and the haemoglobin content, and powerfully /

fully increases phagocytosis. In this finding he agrees with Rogues.

Antimonium Tartrate which has been used with such great success in the treatment of Kala Azar, has also been tried in cases which have proved resistant to Quinine. A one per cent solution of the drug in distilled water is prepared, and one c.c. of this is injected, very slowly, intravenously. The immediate effect of the injection is often giddiness and tingling of the hands and feet, and if there is any tendency towards Bronchitis in the patient, a mild attack always follows. The dose is repeated every alternate day with a regulated increase of .5 c.c. on each occasion. While the writer has tried it very successfully in some advanced cases of Kala-Azar, he has not given it in cases of Malaria.

Some observers have recorded that cases of Kala-Azar also suffering from Malaria have been apparently cured of the Kala-Azar, but the chronic Malarial condition has remained. Possibly the double infection may render the action of the drug less potent against the Malarial parasite, and in cases of single infection it may yet be found to be of some use.

Mention might be made of Lamballe's²¹ experiments on twelve British Soldiers who shewed severe infections, or were suffering from relapses. All were cases that had resisted Quinine treatment by the mouth. One injection of Trypsin, (1850 Robert's units), and an injection of Amylopsin, (500 units), were /

were given, and repeated in resistant cases until the injections themselves caused a rise in temperature. When this reaction was noted, the patient was considered to be fully under the influence of the ferments, and no further treatment was required. Usually only three injections were needed, and the results were very remarkable. The parasites rapidly disappeared from the blood, even the crescent forms, after the first injections, and there were no relapses. The principle upon which this treatment is based is, according to Lamballe, that the natural protective ferments of the host react against the asexual phase in the life history of the parasite, and sexual forms appear. As these ferments are insufficient to destroy the more resistant sexual forms, the disease recurs. Thus the natural method of destroying these gametes would be by increasing the normal ferments. This is done, artificially, by the injection of the Pancreatic ferments Trypsin and Amylopsin.

Splenectomy - In cases of enlarged spleen following on Malaria, the operation of Splenectomy has been advocated. This operation was first performed by Kuchler²² in 1885, but with a fatal result. Dorsay²³ was the first to perform the operation successfully, and Kopylow²⁴ recounts 13 cases with a mortality of 16% to 60%. In successful cases the results are good, the patient being able to resume work, although even this heroic procedure does not exempt the subject from relapses, which occurred in three cases. Castelari²⁵ reports /

reports one successful case which was followed by a relapse. The condition of the blood, as evidenced by the rise in haemoglobin, and in the number of the red blood corpuscles, was improved ; but there was little change in the differential leucocyte count, or in the total number of leucocytes. Similar results were obtained by Degorce.²⁶ One successful case was followed by a very severe relapse, which was extremely resistant to Quinine even when given by injection. This author concludes that Splenectomy is only justifiable in these cases where the enlargement involves much suffering, or where it is so friable that a slight injury may cause rupture. He believes that the extirpation of the spleen interferes with the defensive mechanism of the organism.

X Ray Treatment. Irradiation of the spleen in Malaria has been tried successfully by McCulloch²⁷ in three cases of hypertrophied spleen in Europeans in 1907-8. Skinner and Carson²⁸ tried it in cases in which fever was actually present, and found that there was an immediate relief of the splenic pain, reduction of the temperature, which did not as a rule rise again, and a diminution in the size of the spleen provided this were of recent origin. Of the five cases reported, some had already proved resistant to Quinine, but promptly yielded to the X Rays. Cases of chronic induration, however, proved to be very resistant. In one case treated by Quenu and Degrais,²⁹ the application of the rays caused some cutaneous irritation, and a little pain, but effected a rapid reduction of the spleen

and improved the character of the differential leucocyte count. The parasites in this case were not found in the blood, although the enlargement was undoubtedly caused by malaria.

CINCHONA DERIVATIVES IN THE
treatment of.
MALARIA.

While all these methods of treatment are of great interest to the experimenter in the laboratory, they have not proved themselves to be of practical value to the ordinary Tropical Practitioner, and it is doubtful if any of them will replace Quinine from the position it holds as being at once the most readily administered, easily procurable, and thoroughly efficient drug in the treatment of this terrible scourge.

For the ideal treatment of any fever certain general conditions are required. Amongst these may be mentioned rest in bed, good ventilation, light diet, warmth and quiet. Yet in India, and more especially amongst the village population, who form by far the largest number of our patients, nearly all these requirements are absent. It is no uncommon thing to see one of the cow-boys stop in his play or work, to seek the shelter of some tree or verandah, where he lies down for a few hours, until the attack of fever passes off. School children often simply lie on the bench at one end of the school-room, until they are well enough to resume their studies ; and it is exceedingly difficult to make the people understand that what one day appears to be only an attack of simple fever, may, on the next occasion, produce a fatal result. In cases of severe fever on the other hand, the patient is compelled to remain in bed it is true, but the doors and windows are carefully closed, and the air, which is already /

is already confined and close, is used up by a crowd of anxious relatives ; while, too often, the diet is regulated by the whims of the patient. Under such conditions the wonder is, not that there are so many deaths from Malaria, but that the actual case mortality is so low.

Even in the case of Europeans in India, the conditions are far from ideal. Owing to the shortage of hands every one has more than his share of work, and when one of the number takes ill with fever, he works as long as he possibly can, and sometimes resumes work as soon as the fever shows signs of leaving him. All these things tell against the treatment of Malaria ; and yet in spite of these drawbacks great success has been attained.

The experience of the present writer has been practically limited to the derivatives of Cinchona bark, viz:- Quinine, Cinchona Residual Alkaloid, Quinoidine, and Cinchonine. The method of the Preparation of these drugs is as follows:- The bark of the roots, trunk and stems of the Cinchona tree is stripped off, dried and powdered. This powder is mixed with quick lime and just sufficient water to make it moist. The lime renders more easy the subsequent extraction of the alkaloids. This mixture is kept for two days, then it is made into a thin paste with water and put into vats. Caustic Soda and Mineral Oil are now added, and the whole is mixed thoroughly and heated to 170°F. For half an hour /

hour the contents of these vats are kept at this temperature and constantly stirred. The mixture is now allowed to settle for an hour, and it separates into two layers - the upper layer contains the oil with all the alkaloids dissolved in it, while the lower layer forms the "sludge". The "Alkaloid-oil" is decanted into separators, and mixed with dilute Sulphuric acid. No artificial heat is applied, as the fluid is still warm from the vats, and the mixing with it of Sulphuric acid generates additional heat. The solution in the separators is allowed to stand for two or three hours when two layers are again formed. The acid or lower layer containing the Quinine is drawn off into troughs, heated and exactly neutralised by Caustic Soda. On cooling, crystals of quinine sulphate separate out. The whole is now run off into a centrifuge, which consists of finely perforated copper, lined by a layer of cloth on which the Quinine Sulphate accumulates. The liquid which is strained off from the centrifuge is collected, and from it the other Alkaloids are obtained. This fluid is mixed with Caustic Soda and the alkaloids it contains are thus precipitated, and form the Residual Alkaloid. This last differs from "Cinchona febrifuge" in being derived from a different bark and in containing different relative proportions of the alkaloids. "Residual Alkaloid" is prepared from a bark rich in Quinine ("Cinchona Ledgerina"), but, as this latter Alkaloid has already been extracted in the first part of the process, little of it re-

mains. "Cinchona febrifuge" is prepared from a bark poor in Quinine (Cinchona Succirubra), but it contains all the Quinine as well as the other alkaloids.

Quinine :- Ever since the discovery in the Sixteenth Century of its specific action upon Malarial fevers, Cinchona bark or one of its derivatives has held the foremost place in their treatment. Quinine has been the most popular of these, and there has been no drug hailed as a specific for any disease that has retained the confidence of the profession for so long a time as Quinine. It may seem a truism to say that no treatment should be begun until the diagnosis has been made ; but when one reads that in order to eliminate Malaria from the diagnosis of any fever of uncertain origin, Quinine should be given in full doses, and if the fever resists this treatment, then it is not a case of Malaria, one feels that the remark is not uncalled for. No young practitioner in the Tropics should rest satisfied until he has learned to diagnose Malaria from finding the parasites in the blood. Half an hour spent every day in examining likely bloods will, in a very few weeks, enable any one of average intelligence to recognise the parasites. The Quartan forms are the most easily diagnosed, but with some practice the various forms of the parasite at any stage of their cycle may be recognised, and even the degenerate forms which follow the imperfect administration of Quinine, can be readily distinguished.

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With the ordinary Leishman's stain one does not get the highly coloured nucleus that one sees so conspicuously in the text-book diagrams ; but the peculiar translucent hyaline effect which the protoplasm of the parasite gives to the corpuscle, when once recognised, will be unmistakable. Of course the easier method is to have the parasite demonstrated to one in the different types of plasmodial infection, and we think that the time is not far distant when it will be insisted on, that every Practitioner who intends practising in the Tropics, should first of all learn to diagnose this disease from the microscopic picture. Further, in the progress of the treatment it is advisable that the effects of the drug be controlled by daily blood examination and the treatment should be continued until slides taken on a number of consecutive days are entirely free from the plasmodia, or their crescentic forms. The writer has noted that in these cases where there are very few parasites, these are generally to be found grouped round the large white Corpuscles - a point to which attention has not yet been drawn. A further help in doubtful cases is found in the presence of a leucopaenia with a relative increase of the large Mononuclears which occurs in every untreated or imperfectly treated case of Malaria. The pigment, too, should be looked for in the large Mononuclear leucocytes, and the urine should be tested for Urobilin. These tests, together with the clinical picture, make the diagnosis an absolute /

absolute certainty, and nothing less than this should satisfy the Practitioner.

Quinine acts more quickly and more effectively if the first dose is given in combination with a mild purgative, such as a dose of Salts or Calomel, and taken on an empty stomach ; but neither of these conditions is essential. The main effort should rather be directed towards bringing the patient under the influence of the drug, as soon as possible. Manson³⁰ recommends waiting in ordinary cases until the sweating stage is entered upon, before giving the first dose of Quinine. The sole reason for this is to prevent the patient having the discomforts of Cinchonism added to those incident to the fever. The writer, however, has found by experience that the discomforts of Cinchonism are rarely felt when the temperature is high, and that the sooner the Quinine is given in all cases the better. The delay of a few hours, until the temperature is reduced, may mean that the parasites are not sufficiently destroyed to prevent a succeeding attack. Further, Craig³¹ has demonstrated that Quinine affects the parasites at every stage of their existence, and not merely during the sporulation period (as was formerly held) when, for a short time, the young plasmodia are free in the blood; therefore the sooner they are weakened and destroyed by Quinine the better.

Dosage: There are two main methods of administering Quinine, both of which are supported by authorities.

Manson /

Manson gives it in the comparatively small doses of five grains repeated at intervals of six or eight hours, for the first week, and after that three times on one day a week for the next five or six weeks. The writer modifies this by giving four grains every four hours for the first week, and then he gives four grains night and morning for one month.

³² Torti advocates the administration of a single dose of fifteen grains some hours before the expected ³³ paroxysm, while Sydenham gives a similar dose on the decline of the fever. The objection to this method lies in the fact that some patients who can readily tolerate Quinine when given in small doses are completely upset with sudden large ones; and the writer has met with cases of permanently impaired hearing, which were due to the administration of single large doses of Quinine. Further, in cases of Malignant infection, with irregular fever and no rigors, it is by no means easy to detect either the onset or the decline of the paroxysm, and while waiting for this much valuable time may be lost.

Modes of administration - Oral Administration :

Quinine Sulphate should, if possible, be given in acid solution, but the Byhydrochloride is soluble in plain water. If the bitter taste is objected to, the powder should be given with milk, after the mouth has been lubricated with a little bread and butter, as advocated by Manson. If the Sulphate is dissolved in Hydrobromic acid instead of dilute Sulphuric /

Sulphuric the headache, and other trying symptoms of Cinchonism are considerably lessened. Tabloids or tablets, if properly made, form a convenient mode of giving Quinine, and in ordinary cases they are very efficient. In cases where the digestion is weak, however, and the tongue furred they should be crushed before being administered. Children or fastidious patients may be given Euquinine with advantage ; for although it is not so rapid in its action, it is just as effective, and has the great advantage of being practically tasteless. For a child one year old, one grain mixed with a little sugar, should be given two or three times a day, and the treatment continued for three weeks after the fever has abated. Euquinine may also be given in pregnancy in doses of two grains every four hours. Quinoidine in two grain doses given repeatedly is better still ; but is now unobtainable. This drug seems to have less action on the pregnant uterus than Quinine.

Rectal administration : This has been advocated where Quinine cannot be taken by the mouth, but the writer's experience of this method has not been very successful as there was considerable discomfort in retaining such an irritating injection. The injection if made should contain double the dose in dilute solution that would have been given by the mouth. It should be combined with ten minims of Tr. Opii, and injected high up.

Intramuscular Injection /

Intramuscular Injection : In all cases where rectal administration might be called for, we have a far more effective method in intramuscular injection. It should be resorted to in the first instance in all cases which either by the clinical symptoms or by the microscope shew a heavy ~~per~~ pernicious infection or the "ringed red cells" described by Sergeant³⁴ and others. As a rule one injection is sufficient, and the treatment should be continued by oral administration. In only one case where quinine was not tolerated by the mouth, was it found necessary to give the patient a course of injections. The practice of the writer differs in one important detail from that usually advocated. After sterilising the syringe by boiling, and painting the skin of the front of the upper arm with tincture of iodine in the usual way, the needle is plunged boldly into the Biceps muscle, and the piston pressed slowly home. After the injection the part is very thoroughly massaged both with superficial rubbing and deep pinching for at least ten minutes. This insures that the quinine is thoroughly diffused through the muscle and leads to its ready absorption. The massage should be repeated night and morning for 3 or 4 days. As a result of this procedure we have not had a single case of abscess, following intramuscular injection. To leave a mass of undiffused Quinine in the tissues is to court future trouble. The question of absorption is one over which authorities differ. Ross maintains that the /

the Quinine remains in the muscle, and is not absorbed.
 Manson on the ^{other} hand believes that the efficacy of this mode of administration is undoubtedly due to its absorption. MacGilchrist in a series of experiments on animals found that the quinine is absorbed although slowly. The writer made a series of experiments recently to determine this point. In each case five grains of the Bihydrochloride of Quinine were injected, and the effects noted. It was found that both in cases of Malaria and in healthy subjects, the symptoms of absorption, as shewn by tinnitus, were always discernible within half an hour of the injection. The Quinine is therefore absorbed, and it has been proved by the experiments of MacGilchrist, that this process, although it begins without delay, proceeds gradually, but continuously for some four days, during which time the drug is being slowly excreted by the urine, as shewn by the Ammonia test. The experience of most Tropical Practitioners undoubtedly supports Manson in his statement that in this particular mode of administration we have a most potent weapon against the parasite. The question naturally arises, why is this mode so popular, that it forms one of the chief methods in all cases where a rapid and certain result is necessary ? The answer to this is found in the action of the drug when introduced into the system in small doses. In large doses Quinine undoubtedly paralyses the white blood corpuscles, but in small doses it greatly stimulates phagocytosis.
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When Quinine is injected intramuscularly, it is absorbed slowly so that it causes a great increase in the power of the leucocytes to deal with the parasites. The parasites meantime have been weakened by the direct lethal action of the drug. For the recent experiments of MacGilchrist⁹ have shewn that prolonged, continuous exposure of *Paramaecia* to Quinine Solution renders them more sensitive to the action of subsequent lethal doses. Further, this injection is an intense irritant, as any one who has been subjected to this form of treatment knows, and, like any other irritant, it sets up an immediate leucocytosis. Thus both by augmenting the number of leucocytes and by raising their efficiency this mode of giving Quinine is most effective. The writer has already noted when dealing with Ethyl-hydro-cuprein that when given intramuscularly it is extremely effective. Another authority, (Baermann) said that when injected intravenously, the results were disappointing, and stated that the intramuscular injection is accompanied by an intense local reaction - in other words a great degree of leucocytosis was set up. Its efficacy is due, ^{so much} therefore, not to the lethal effect of the drug, ~~as~~ to its irritant local action. This is also one explanation of the effectiveness of intramuscular injection of Quinine. There are three modes of dealing with the parasites so as to diminish their virulence (1) by the direct lethal action of the drug on the parasite; (2) by increasing the phagocytic

phagocytic action of the leucocytes and (3) by increasing the number of the leucocytes. Quinine by the mouth in large doses acts only in the first of these ways. Hectine, which according to Crespín, causes an increase in the phagocytic action of the leucocytes; may be taken as an instance of the second; while Quinine, injected intramuscularly combines all three. It is to this that it owes its peculiar efficacy.

The site of the injection is important. Most text-books and writers advise the Gluteal region, but the present writer some years ago injected Quinine into the Biceps muscle, and found it so convenient and effective, that he has continued to prefer that site. The main reason for choosing it is the ease and efficiency with which deep massage can be performed. Difficulty had previously been experienced in thoroughly distributing the Quinine solution throughout the Gluteus muscle; but no such difficulty presents itself in the case of the Biceps. A further reason appeals to the Indian, who delights to sit on his heels on the verandah as soon as he is able to crawl out of bed. The tension produced over the gluteal region by the injection causes unbearable discomfort on attempting to assume the favourite posture. This may seem a small matter, but the average Indian would sacrifice his health to his comfort, and one naturally prefers a method which, while no less effective is not open to this objection.

Subcutaneous /

Subcutaneous Injection : Of the subcutaneous injection dilute solutions, as advocated by James, the writer has had no experience. On the two occasions on which injections of the usual strength were given subcutaneously, the patient suffered from paresis of the sensory nerves of the injected area. Thus, in the forearm, when an injection was made over the Supinator muscles, the whole of the radial border of the forearm was rendered completely insensitive to pain, and this loss of sensation lasted for several weeks, although the area involved gradually diminished. This confirms the findings of MacGilchrist that Quinine acts as a local analgesic as effectually as if the nerve had been resected. It is also interesting to notice that the Urea and Quinine Hydrochloride salt has been used not only as a local anaesthetic, but also as an anti-periodic. Its injection is painless, and its action although not so powerful as the Bihydrochloride salt, is still effective.

Intravenous Injection: In cases that have already become unconscious, no time should be lost in giving 8-10 grains of Quinine by this method. The action is certain and rapid, and may be the only way of saving the patient's life. When injected intravenously Quinine should be given in dilute solution. Half to one pint of water should be used to dissolve 8 or 10 grains, and this quantity should be injected very slowly by transfusion. In one case attended by the writer, at the patient's own home, there were no /

no means for transfusion at hand, and the usual concentrated injection was given intravenously. Nothing but good resulted, probably because the injection was given very very slowly. If injected rapidly, there is a great tendency to produce coagulation of the blood.

Amorphous Cinchona Alkaloid or Residual Alkaloid.

In our consideration of the Quinine Derivatives, we have hitherto confined ourselves to Quinine and its salts. But ever since the writer came to the Tropics, Quinine itself has played a very secondary part in his efforts to treat Malaria. During the first two years in India, he was in partial charge of the Ranaghat Mission Dispensary and Hospital situated about fifty miles to the N. of Calcutta in the district of Nuddea, Lower Bengal. The place was one that was notorious for its endemic Malaria, and within a few months of the opening of the Dispensary, the number of patients ran into the hundreds. Malaria was the chief disease, and on making out our statistics, it was found that during the height of the fever season - i.e. from July till December, 90% of the total cases were Malaria ; while 60% to 70% was the average for the so-called Non-Malarial months. Owing to the smallness of the staff to cope with such numbers, the Dispensary was open only three days a week - two days for men, and one for women and children. At first Quinine Sulphate in solution was given $7\frac{1}{2}$ grains three times day being the adult dose, and /

and, although this was quite effective, the drug bill was so exorbitant that search was made for a cheaper substitute.

Cinchona Febrifuge was tried, and discarded as it was not efficient. This result has since been confirmed by Waters.³⁵ One of the staff, (Dr C. G. Monro) then gave Amorphous Cinchona Alkaloid a trial. This proved to be so efficacious that the number already attending the Dispensary increased, and the fresh fever cases alone sometimes numbered as many as 500 in a single day. The returns for the year came to between thirty and forty thousand. The price of the drug was only one fourth, that of Quinine Sulphate, and as the dose is somewhat smaller, the saving effected by its adoption was enormous. It only needed a few weeks trial to convince one that in Amorphous Cinchona Alkaloid, one had a remedy even superior to Quinine in the rapidity and reliability of its action. Thus the drug, that was used at first on account of its economy, has retained its position because of its efficiency. The results have been so uniformly good that for years we have hardly used any Quinine at our Dispensaries in the treatment of ordinary fever cases, and our example has been followed by many of the Medical Missionaries throughout India, no one of whom has reported unfavourably on this drug. Not only was Cinchona Alkaloid (or Amorphous Alkaloid as it is sometimes called) found efficient in all the ordinary forms of Malaria, but also in that form of low fever which seems to be produced in Bengal by the

the action of the Climate apart altogether from Plasmodic infection. This fever is most intractable, and Quinine seems to have no effect upon it. At the close of his second year in India, the writer was unfortunate enough to contract this form of fever, and again ten years later he had a similar attack. On this latter occasion his blood was examined repeatedly for the parasites of Malaria, but none were found. He had tried Quinine, Warburg's Tincture and a variety of other drugs including Arsenic and Iron, but without avail. Finally Cinchona Alkaloid was tried, and within a week the daily afternoon rise of temperature ceased, and a complete cure followed. Since that time several similar cases have been successfully treated.

Mode of Administration; The writer has always employed Cinchona Residual Alkaloid in solution, but others have had very good results from giving the dry powder in 5 grain doses. The stock solution for Dispensary use is made as follows:- Three and a half ounces of the Cinchona Alkaloid are mixed thoroughly with one pint of water. To this mixture One ounce of strong Sulphuric Acid is added very slowly while stirring briskly. Another pint of water is then added, the mixture stirred well, and either filtered through cotton wool, or else allowed to settle, when the supernatant fluid may be decanted or syphoned off. The adult dose of the resulting solution is one drachm well diluted, although as a rule slightly larger doses are given at the commencement

ment of the treatment. The amount of Alkaloid contained in each dose is just over 5 grains, and this dose is given three times a day irrespective of the time when the fever is due - the idea being to saturate the blood of the patient as rapidly as is compatible with safety.

To the European patient, the chief objection to this preparation is the obnoxious smell and taste. This may be overcome by giving it in dry form in a cachet followed by a tumblerfull of water or of dilute Sulphuric Acid solution (1 m. to the ounce.) The writer has found from practical experience that both the smell and taste are to a large extent overcome by the children's expedient of holding the nose, and taking a little common salt both before, and after the liquid dose. Owing to its objectionable taste our Indian Christians were sometimes given Quinine in tablet form. On several occasions it was observed that the patient continued to have the fever, in spite of this treatment ; although it yielded completely to a few doses of the Cinchona.

Alkaloid Solution administered subsequently.

An analysis of the Constitution of Amorphous Cinchona Alkaloid gives us the clue to its peculiar efficacy. According to the Government Quinologist of India, the residual Alkaloid left after the quinine has been extracted, is really an amorphous mixture of all the Alkaloids of Cinchona bark, and was originally treated as a bye-product. The average /

average composition - for it varies slightly in different samples - is as follows:-

Quinine	-	3%
Cinchonidine	-	2%
Quinidine	-	20%
Cinchonine	-	35%
Quinoidine	-	30%
Water, ash etc.	-	10%

Although each of these alkaloids is antiperiodic in its action, yet this combination is peculiarly so. MacGilchrist⁹ in his recent investigations upon guinea-pigs and paramoecia referred to above, has thrown light upon the subject. Of all the derivatives, Cinchonine was found to be only slightly more lethal to this host than quinine, while being much more lethal to the parasites. The results of his experiments are given in the following tables:-

I. Minimum lethal dose for guinea pigs by the mouth:-

Sulphate of Cinchonidine	.6	gramme	per kilo	of animal	weight.
" " Quininae	.525	"	"	"	"
" " Cinchonine	.425	"	"	"	"
" " Quinidine	.4	"	"	"	"
" " Quinoidine	.35	"	"	"	"

Thus Cinchonine is slightly more lethal to guinea pigs than quinine in the proportion of 4 to 5.

II. Minimum Lethal concentration which kills all varieties of Paramoecia.

Cinchonine Sulphate	-	1 - 140,000
Quinine Sulphate	-	1 - 100,000
Quinidine "	-	1 - 100,000
Cinchonidine "	-	1 - 60,000
Quinoidine	-	1 - 80,000

Cinchonine, from these experiments, is more effective as a toxic agent against infusoria than Quinine in the proportion of 7 to 5.

In a further series of experiments these results were confirmed or modified in actual clinical tests

tests; Cinchonine was found to be more effective than Quinine. The writer has used Cinchonine in small doses for children when, owing to the recent war, the price of Euquinine was prohibitive. The taste is not nearly so unpleasant as Quinine, and can be suitably disguised in a little sugar. In several cases in adults the fever responded very rapidly, and no relapses were recorded. It is probably owing to the large percentage of Cinchonine present that Residual Alkaloid is so efficient. Its preparation from Cinchona Residual Alkaloid depends upon its comparative insolubility in Alcohol.

Quinoidine. The only other drug with which the writer is personally familiar in his treatment of Malaria is Quinoidine. This drug was first used by Sethuner in 1830 who found it superior to Quinine. Prain in 1902 confirmed these results. But up till 1913 little use was made of this knowledge. In 1913 Waters³⁶ published his results in which he stated that he found Quinoidine 3 to 5 times more effective than Quinine. He found that an average of 16 grains in 2 gr. doses was sufficient to cure any type of Malarial fever. MacGilchrist³⁷ criticised Waters experiments pointing out that the dose was too small, and further, that the absence of temperature alone was no indication of the cure of the patient. The microscopic test was applied by MacGilchrist in his more carefully-conducted experiments. They shewed that Quinoidine, although ultimately effective, was less speedy in its action than Quinine. The writer used /

used Quinoidine in 2 grain tablet forms, very extensively. The adult dose was two tablets, i.e. four grains three times a day, and the effect was so uniformly successful in his Dispensary practice, that patients began to ask for the "Black pills" as they called the Quinoidine tablets. One point specially noted by the writer was found in connection with cases which had been treated by Quinine by Indian Practitioners. These cases always responded to Quinoidine very rapidly, and it would seem that this drug acts most rapidly in those patients whose parasites have already been weakened by exposure to Quinine. Probably the combination of Quinoidine with Cinchonine in Residual Alkaloid is one of the main factors that render that preparation so potent in its action. It is now no longer obtainable.

The writer has been handicapped throughout his investigations in these drugs by the fact that his patients, whether in Hospital or attending the Dispensary, ceased treatment as soon as the fever was in abeyance. This hindered the final and conclusive microscopic test being applied, which defeats to some extent the scientific accuracy so much required of us all in these days. Still, the clinical test is borne out in the case of other antiperiodics by the microscope, and we may reason, by analogy, that Cinchona Residual Alkaloid would pass the blood test, just as efficiently as it acts on the temperature. Before leaving this part of our thesis, we should like to touch briefly upon one or two cognate subjects. The

The first of these is the so-called "Quinine-fast" parasite. It has been noted that if a patient is receiving Quinine in insufficient doses, subsequent increase of the dosage seems to have no effect on the parasites. The reason that has been brought forward is that the parasite has accommodated itself to living in a dilute solution of Quinine, as it were by an "acquired or artificial immunity."

MacGilchrist's experiments with infusoria proved that as far as they were concerned no such immunity was noticed. If the Paramoecia were exposed to a very dilute solution of Quinine for 12 hours, it was found that they were very greatly weakened, and a dose of less than half the minimum lethal dose of Quinine was sufficient to complete their death. Similarly in the clinical experiments conducted by him in the Presidency Jail, Calcutta, he found no cases of "Quinine fastness" or relative resistance. The explanation of such cases according to this authority, is that the Quinine has not been given continuously, and the parasites, still lurking in the system, recommenced sporulation, and were found in the blood, at a later date. Even small doses of Quinine (2 grains) if given frequently, i.e., every two or three hours and continued for one week was sufficient to rid the system.

Secondly, there is the Antipathy of the Indians to Quinine. In spite of the facts that for years Quinine has been recognised as the specific for fever, and that it has been advertised widely and distributed /

distributed freely by the Indian Government, this drug is by no means popular with the natives of Bengal. There are several reasons for this antipathy. In the first place there is an old standing prejudice amongst all the older Bengali Practitioners, that until the temperature reaches normal, no Quinine should be given. In Subtertian infections it is no uncommon thing for the temperature to remain above 100° for 20 out of the 24 hours, and the defervescence of the fever generally takes place between the hours of 12 and 4 a.m. - a time when as a rule no Bengali Practitioner visits his patient, and no one else will probably trouble to take the temperature. Hence Quinine may be withheld during the whole of an attack, although at any moment serious symptoms may develop, and the case end fatally. Possibly one or two doses of Quinine given when everything else has failed, will receive the blame for the fatal issue. Even in cases that have been treated thoroughly with Quinine there is another reason for this prejudice. Before the identification of such continued fevers as Typhoid, Para-typhoid, Kala-Azar and Malta fever, all were included under the name "Malaria". Quinine was given without any appreciable effect, and was therefore pronounced useless in the treatment of certain forms of Malaria, - an impression not easily eradicated from the Bengali mind. But perhaps the chief reason is to be found in the poor results following the lack of continued treatment. How many Bengalis are there, even amongst the /

the most educated, who will continue to take Quinine even for one week after the temperature has been controlled ? The result is a relapse in a week or two, and Quinine is blamed. Old prejudices die hard, and it will be a long time, even with efficient treatment and instruction, before the Bengalis entirely rid themselves of their present antipathy to Quinine.

Another matter upon which sufficient emphasis has not been laid is the necessity for early treatment. The writer has noticed that one dose of medicine given as soon as the prodromata are manifested, and before the temperature rises is often sufficient to ensure a complete cure. One Medical Missionary in India was cut off from the supply of Quinine for some weeks during the height of the fever season, and yet, by the administration of a single dose of gr. X. to each patient with instructions that it be taken 2 hours before the expected attack, he was able to carry on successful treatments with a very limited amount of Quinine. In the case of a first attack the prodromata are not usually recognised by the patient, and the Physician is not called in until the febrile stage has been reached. No time should be lost in commencing treatment, preferably by small doses repeated at frequent intervals. In the case of recurrent attacks the prodromata which frequently take the form of headache, irritability, and general lassitude, are readily recognised, and two doses of

4 or 5 grains of Quinine will then be sufficient to ward off the attack.

The conclusions arrived at by the present writer regarding the treatment of Malaria may be summed up in a few sentences. Malaria in all its forms can be treated efficiently by Cinchona derivatives especially by the Residual Amorphous Alkaloid. The treatment should be begun as early as possible, continued in small doses at frequent intervals, and should last for at least one month, even in the non-Malarial seasons.

Treatment of Complications.

Hitherto our attention has been confined to the treatment of uncomplicated cases of Malaria, and, although these form by far the largest number of our cases, yet not infrequently complications which require special treatment accompany or ensue upon an attack of Malaria. The more important of these are:- Hyperpyrexia, Cerebral Symptoms including Coma, Choleraic and Dysenteric complications, Pneumonia, Splenomegaly, Anasarca, Nyctalopia and Anaemia.

Hyperpyrexia : A temperature of over 105°F. in an otherwise uncomplicated attack of Malaria should be regarded as calling for special and immediate treatment. A hypodermic injection of 5 gr. of Quinine should be at once administered, and some antipyretic such as Phenacetin or Acetyl-Salicylic Acid given by the /

the mouth. Antifebrin may be given in gr. I. or II. doses every 2 hours. But whatever the antipyretic used, a careful watch should be kept on the pulse, so that dangerous collapse may be avoided when the temperature falls. On the first signs of collapse, an injection of Digitalin or Strychine should be given.

Another, and less dangerous method has given very good results in the hands of the writer. Creosote when applied externally has a wonderful influence in reducing the temperature. The action is difficult to explain, but it has been found that 3-5 minims of Creosote oil rubbed well into the axilla or inner side of the thigh has an almost immediate effect in bringing down the temperature.

Placing the patient in a bath of tepid water, and gradually lowering the temperature to 60F. has been advocated, but the writer has never had occasion or opportunity to test this method, nor that of applying cold packs.

Cerebral Symptoms. Mental aberration, tremors, restlessness and sleeplessness should always be looked upon as serious in cases of Malaria. As soon as these symptoms manifest themselves an immediate Hypodermic injection or better still Intravenous injection of gr. X. of Quinine should be given. Convulsions and Coma must be similarly treated in an energetic manner. The prognosis in these latter cases is much brighter in children than in the case of Adults, although even in these recovery is not unusual.

Choleraic & Dysenteric Symptoms should be treated by intramuscular injections together with the administration of Bismuth & Opium by the mouth. The diet should be restricted to ice and soda water for twelve hours, and the return to the usual fever diet should be gradual. All movements on the part of the patient should be ^{as} restricted as possible.

Pneumonic symptoms yield rapidly to an intramuscular injection of Quinine, and the oral administration of Creosote in these cases has proved exceedingly beneficial. During the cold season it is not at all an uncommon complication in Bengal.

Splenomegaly resulting from Malaria is of two kinds.

1. The moderate enlargement, not usually exceeding two or three finger-breadths below the ribs, which occurs after a fresh attack of Malaria. The spleen is soft, the fibrous tissue is not increased, and the reduction in size is readily effected by treating the Malaria as already indicated, and building up the system with Iron and Arsenic.
2. The other form is the result of repeated and prolonged attacks, and is the enlargement, which, especially in children, characterizes the "Endemic Malarial Index." In some cases the enlargement seems to occur without any definite attacks of fever, although there are numerous parasites in the blood. It differs from the Splenomegaly of Kala-Azar in being slower in formation and in not usually attaining such a large growth. Still, it is not uncommon in cases of undoubted Malaria to find the spleen /

spleen reaching well beyond the Umbilicus. The treatment of such cases is long and tedious, but patience and perseverance will be rewarded by a complete cure. After the 'fever' has yielded to treatment, the system must be toned up, and for this there is nothing better than the 'Sulphate Mixture' or one of its modifications:- Sulphates of Quinine, Iron and Magnesia together with Arsenic, and if there is any tendency towards Anasarca the addition of Spirits of Chloroform. In our own practice we substitute Cinchona Alkaloid for the Quinine. This mixture clears the blood of parasites, raises the number of Red Blood Corpuscles, increases the Haemoglobin content, and causes a moderate amount of Leucocytosis - all of which help in restoring the general health. For local treatment, the skin over the spleen used to be cauterised, and painting this area with Tincture of Iodine is still favoured in many quarters. There is, however, at our command a more efficient method in the subcutaneous injection of Muir's. "T.C.C.O." mixture which he has used with such good results in the treatment of Kala-Azar. This mixture consists of one part each of Turpentine, Camphor, Creosote and two parts of Olive oil. Three to five minims of this mixture is injected over the spleen which is repeated every seven or ten days. The effect is that of an intense irritant, producing /

ing a well marked leucocytosis; while the counter-irritation has a reflex effect upon the spleen itself. Further, the skin over the edge of the tumour is outlined with a very fine pencil dipped in pure Carbol-ic, and the 'outline' filled in by painting the whole area with tincture of Iodine. This 'outline' of pure Carbol-ic serves the double purpose of counter-irritant, and delineation. The patient himself can see the progress week by week, and as a rule 3 or 4 months are sufficient to cure the largest spleen.

Anasarca usually takes the form of swollen feet in chronic cases, which in advanced cases develops into ascites. It is only part of the general debility, and is accompanied by dilatation of the heart. It is very seldom that these cases require tapping or the use of Southey's tubes. The line of treatment which the writer has found most beneficial has been a 'dry' diet, with little or no common salt in the food, Magnesium Sulphate in doses sufficient to produce 2 or 3 loose stools every day and the 'Sulphate Mixture' with Spirits of Chloroform and Strychine.. Injections of Digitalin may be necessary in advanced cases with threatened heart failure. If patients in such an advanced condition can be tided over the first week of treatment, they make a good recovery.

Anaemia is one of the most common aftermaths of prolonged or repeated attacks of Malaria. This is produced not merely by the destruction of the individual corpuscles by the parasites, but also by the general effect /

effect on the blood of a toxin generated by the parasite. This is best treated in the European patient by a change either to a non-malarious district, or ^{by} the hills, or/a sea voyage. But when this is impossible, as with the vast majority of Indian patients, the Sulphate Mixture with Arsenic, or Iron in the 'Scale' preparation and Quinine should be taken for about a month. In any case which does not yield readily to this treatment Hookworm Disease should be suspected.

Nyctalopia - A peculiarly trying complication of this profound Anaemia which is met with especially in the wandering coolies of India is Night Blindness. Immediately after sunset these people are plunged into complete darkness, and are unable to move unless helped by their neighbours. The etiology is generally to be found in faulty nutrition and exposure - such as are incidental to this class of people. In ^{the above} addition to/tonics the writer has found great benefit from the daily dropping into the eye of one or two minims of Cod Liver Oil. The benefit is immediate and lasting. A few applications are all that is necessary. The method of action is obscure, but probably there is some connection between the injection of the conjunctiva which this treatment produces, and the increase of the blood supply to the retina.

Relapses. The cause and treatment of relapses form two of the most difficult problems in the whole study of Malaria. Three theories have been advanced to account for their occurrence.

The Parthenogenetic Theory advocated by Schaudinn, attributes the relapses to the sporulation of the unfertilized macrogamete. This sporulation has undoubtedly been observed by one or two investigators, but not sufficiently often to account for the frequency of relapses. Ross has opposed this theory mainly on the experiments of Thayer and Elting who on four separate occasions injected only sexual forms into the blood stream of healthy individuals. Three of these were entirely negative both as regards parasites in the blood and clinical manifestations. While the fourth case had a slight rise of temperature on the 2nd and 6th days after the injection, but there were no parasites found in the blood.

The second theory is the Intra-corpuseular Conjugation of the young ringed forms, and is held by Craig. This never occurs during the first few days of an initial attack, but in persons possessing a relative immunity the process may take place before any symptoms of the disease have become apparent. This theory is supposed to account for the relapses at long intervals, e.g. one or two months.

The third theory - held by Ross & Thomson is that schizogony continues in the body long after the cessation of clinical symptoms, and even after the disappearance of the asexual forms from the peripheral blood. In a series of examinations it was found that the asexual forms became fewer and fewer, and then disappeared, altogether for four or five days, only to reappear and increase steadily in numbers. When /

When this increase reached some hundreds per cubic, millimeter a 'relapse' set in. The time occupied in this increase would vary with the normal resisting powers of the individual, and the amount of Alkaloid given in the treatment. This would account for the difference in the period which elapses before a recurrence of the clinical symptoms. Additional support has been recently given to this theory by the clinical experiments of MacGilchrist³⁷, who found that after the parasites disappeared from the peripheral blood, they were still to be found sporulating in the spleen. He cites James, who found both sexual and asexual parasites in the bone marrow and spleen of patients who had died from other diseases, although their peripheral blood had been free from parasites while under observation. He believed that the slower blood stream in the sinuses of the bone marrow and spleen afforded the parasites the necessary protection from the Alkaloid, which permeated the system where the blood stream was rapid. He found, further, that the Alkaloids themselves act as vaso-constrictors to the nutrient vessels supplying the bones and marrow. This diminishes the amount of blood to the parts, and causes a still slower blood stream.

MacGilchrist's findings on relapses may be summarised thus:- They occurred most frequently in Benign Tertian cases, and then in Malignant Tertian. In the latter cases relapses were more frequently found in those that had shewn crescents. When the Alkaloids were given in large doses (X. or XV. grains per 11 stone

body-weight) 10% of the cases relapse, when in small doses, i.e. I. or II. gr. only 5%. In these latter cases the treatment was prolonged for several days longer than the former. Crescents were found in 30% of the cases that relapsed. Cases treated with Cinchonine shewed fewest relapses. Early treatment also diminished the number of relapses.

The writer has been greatly handicapped by not being able to follow up his cases. MacGilchrist having to deal only with prisoners in the Government Jails in Calcutta had the great benefit of having all his cases under his control as long as he desired. But the comparatively small number of those who returned on account of a relapse confirms the writer in his opinion that the Residual Amorphous Alkaloid is far more efficient than Quinine in preventing relapses, and this efficiency is due in large measure to the Cinchonine in that preparation.

With our present knowledge the surest way of preventing relapses is by early treatment of every initial attack with small doses of Quinine or Residual Alkaloid at frequent intervals (e.g. gr. IV. every 4 hrs) for one week, followed by 4 grains night and morning for other three weeks.

The importance of early treatment is accounted for in three ways. In the first place, all the natural resistance of the patient, which in many cases would of itself lead to a cure, is very little impaired at the beginning of the attack, and this is of the very greatest assistance in rendering effective /

effective the treatment by drugs. Every succeeding rise in temperature weakens this resisting power and renders less assistance to the action of the Alkaloid. Further, if the system is thoroughly brought under the influence of the drug while the fever is still at its height, and the vital powers are strong, the increase in force and frequency of the heart beat, and the dilatation of all the blood vessels during the febrile attack prevent any stagnation of the parasite laden corpuscles in such normally sluggish areas as the spleen and bone marrow. It is there that the last remnants of the disease would lurk, and by thus attacking them early, and rendering these places untenable, we strike at the very root of relapses. MacGilchrist has also shewn that if the treatment is begun early, crescents do not form, and this is most important not only in the matter of simplifying the treatment of the case, but in preventing the patient from becoming a source of infection.

The need for continued treatment is evident from the fact that most relapses occur within the first three weeks, but under efficient treatment that period may be safely passed without the fear of such an occurrence. One month's continuous treatment insures the death of all Malarial parasites.

PROPHYLAXIS OF
MALARIA.

II. PROPHYLAXIS of MALARIA.

Introductory. Prophylaxis, will, in the future, play a far larger part in the eradication of Malarial fevers than it has done in the past. With such outstanding examples as the Roman Campagna, Ismailia and the Panama region, there is no reason to despair of even such endemic regions as the plains of Bengal. The conditions in the last mentioned region, however, are peculiarly difficult inasmuch as the country is, as a whole, so flat that little can be done in the way of general drainage. Our hope for the future lies more in the line of the experiments of Bentley, who is flooding certain portions of the country with water, in the hope that by decreasing the ratio of dangerous breeding edge and raising the temperature of the water as a whole to over 80° F., he may be able greatly to diminish the breeding of Anopheles. The results of his experiments are awaited with interest. Should they have proved successful, there is little doubt that the Government of Bengal will take steps to have them carried out in a large scale.

The present writer has not been able to take part in any of these larger schemes such as flooding, fish-cultivation in the rice fields, or the extensive use of paraffin oil as a covering for smaller pools. But apart from these much can be done in the way of personal prophylaxis, and it is to this aspect that the writer would especially direct attention.

Since the spread of Malaria is dependent upon one's being bitten by a mosquito, which in turn has been

infected by man, prophylaxis will naturally aim at the protection of the individual from the bites of the mosquito, the extermination of the mosquito, and the prevention of its infection from man,

One of the best methods of diminishing the bites of the mosquito is the effective screening of all doors, windows and verandahs with wire netting - preferably copper wire, for although this is much more expensive, it is very much more lasting. No. 12 mesh has been advocated, but 16 squares to the inch (i.e. No. 16) affords fuller protection. The screen should be tacked on to the outside of the window frame, and the edges covered with a strip of wood. Double-screened doors should be used, there being a small ante-chamber between the two doors, and all the doors should be closed with springs. The chimneys, too, should either be covered with wire gauze, or where not in use they may be temporarily blocked up. But unless the verandahs also are rendered mosquito proof, the restful habit of sitting out in the verandah in the late evening, will not be possible without running the risk of infection. It is strange that in a province like Bengal, this house-protection has never been widely adopted, and, with the exception of a few of the Planters' houses in the Terai district, the writer has seen no European houses where this wire screening has been done. Possibly the number of doors and windows in the average Bungalow would render the initial cost almost prohibitive at the present time. But the main reason has probably been the desire to obtain /

obtain the maximum amount of fresh air in the stillly hot nights of the rainy season, when even the faintest zephyr is welcomed as an aid to sleep by those who are passing hot and sleepless nights. But whether European Bungalows are ever protected or not, we are safe in saying that house screening will never be possible for the ordinary Indian villager.

Mosquito Curtains are now recognised as essential requirements, not only by the Europeans in India, but by the Indians themselves. If well made, close meshed, properly used, and kept in repair, they afford an excellent protection from the night attacks of the mosquito. Perhaps sufficient attention has not been paid in the past to the suggestion of Ross that an outer single layer of gauze should be fastened around the lower border of the net so that ^{if} the arms or legs of the restless sleeper touch the net, the mosquitoes will still be separated from their prey by the layer of gauze. Mosquito curtains alone are not sufficient for it has been demonstrated by many observers that that Anophelines are most voracious in the hours immediately preceding sunrise, and following sunset, and there are few who care to retire to rest at such an early hour in order to avoid insects. The ankles and wrists, hands, face and neck must all be protected. Gloves and masks are too hot and inconvenient to be worn unless in the open air. But by the simple expedient of wearing two pairs of socks or stockings, and rubbing the exposed parts with an ointment made of one part /

part of Citronella oil (or Eucalyptus oil), and one part of vaseline, the mosquitoes may be entirely kept off for two or three hours. In the hottest weather, when even two pairs of socks would be uncomfortable, comparative immunity may be obtained by wearing special high mosquito-boots or light-coloured socks or stockings. Tan-coloured are even less attractive to the mosquito than white. But more constant protection is afforded by rubbing the back of the bare feet and ankles with the Citronella or Eucalyptus ointment in the evening, before donning foot gear.

Measures to exterminate the Mosquito should be directed against both the larval and adult forms. The introduction into tanks and larger pools of the small species of fish known as "Millions" (*Girardinus Pocciloides*) is a simple and inexpensive means of destroying mosquito larvae. These fish are easily procured in India, and they attack and greedily devour all kinds of mosquito larvae. In the ground near dwelling houses, all depressions that give rise to potential breeding-places should be filled up, and water vessels either for domestic use, or for use in case of fire, should either be covered with gauze or emptied out twice a week. Weeds and undergrowth should be systematically removed from the neighbourhood of dwelling-houses, and burnt with fire.

"Kerosening" the pools must be done every week to ensure success, but this also requires careful supervision, as the oil has a market value to the man who is entrusted with putting it on the pools! Celli has pointed /

pointed out that certain aniline dyes, especially one known as "Larvicide", are very efficacious for this purpose, and they have the additional advantage of being non-volatile and non-poisonous to animals.

Against the adult forms we have such a temporary measure as fumigation either by Sulphur dioxide or by some other form of disinfectant. But this is only of value in a house that is going to be, or is already, screened.

A Mosquito trap is made by lining a box completely with black cloth, and propping the lid very slightly open. Mosquitoes are attracted by the dark shady spot, and when a sufficient number have entered, the lid should be suddenly closed by the withdrawal of the support, and the imprisoned mosquitoes may be killed with chloroform vapour. In the writer's hands this has proved very unsatisfactory. A far more effective method is to use a hanging wardrobe as the trap. The door should be left open an inch or two. The mosquitoes enter it, and settle down. The hands are then covered with a soapy lather, the wardrobe tilted slightly at intervals to disturb the mosquitoes, which are easily caught by the hands as they emerge in twos or threes. The writer once destroyed as many as 500 mosquitoes in a week's time by devoting ten or fifteen minutes a morning to this novel and most useful exercise. The house remained comparatively free from mosquitoes for two or three weeks, when another 'Mosquito hunt' was organised. These measures were, of course taken against /

against all mosquitoes indiscriminately as they are a pest in themselves, quite apart from the danger of the conveyance of Malaria. It is very doubtful if even with all these measures the mosquito factor will ever be entirely eliminated. Attention must be given rather to the prevention of the infection of the mosquito.

Mention has already been made of the usefulness of mosquito curtains as a means of preventing infection from the mosquito, but it is even more necessary that the infected patient should be carefully protected, lest the 'carrying' species of mosquito should bite him, obtain some of the sexual forms, and in the course of a few days infect many others. This probably explains the history of most epidemics of malaria and the occurrence of severe outbreaks in jails and hospitals. In our own hospital we used to be struck by the number of cases which suddenly developed in patients who had come in suffering from other diseases. The source of all the trouble was evidently some Malarial case that had been treated, and gone home, leaving a legacy of infected mosquitoes behind him. Every Tropical hospital should be supplied with good mosquito curtains for the use of small patients, but especially for the use of those who are under treatment for Malaria. All infected patients should be impressed with the danger to others which will ensue if they neglect this simple precaution. All 'fever' patients should be under their nets at sunset, and should not be allowed to leave, except under /

under special circumstances, until after sunrise.

By far the most important aid to the prevention of Malaria is the early and efficient treatment of every case. MacGilchrist has pointed out that the crescents only appear when the asexual forms are becoming exhausted, and as a last defence against total extermination. Their production is analogous to the spore-formation of many bacteria, and like them they are exceedingly difficult to kill when once matured. The same investigator has shewn that even moderate doses of Quinine if given early and continuously, completely check the production of the sexual forms. If these do appear, a few days of further treatment with, if necessary, a slight increase in the amount or frequency of the dose, causes them to disappear from the peripheral blood. Not only the laity, but even the ordinary Tropical Practitioner, unless he has made a special study of Malaria, needs to be taught that the disappearance of the clinical manifestations does not mean elimination of the parasite. Too much stress cannot be laid upon this point, and until this knowledge permeates through the Medical Profession to the laity, there will not be that great advance in the prevention of this scourge that we are entitled to expect from our present knowledge. Continuous treatment for at least one month with blood examinations once or twice a week would eliminate the possibility of latent carriers amongst those thus treated. This is a result which ought to be obtained in the case of every European /

European, and every educated Indian, although it may take some years at our present rate of progress before the ordinary villager will consent to undergo such lengthy treatment every time he has an attack of fever. The Indian Government is helping greatly by the encouragement of lectures on 'Malaria', and the exhibition, outside Post Offices, and other public buildings, of diagrams illustrating the beneficial results of administering Quinine. Much has also been done by the free distribution of Quinine ; but in the instructions accompanying each 'treatment' tube more emphasis should be laid on its continuation after symptoms have abated.

The subject of Quinine Prophylaxis has given rise to much discussion in recent years. The results in some instances especially in some Indian jails, have been extremely encouraging, whereas under other conditions, especially in the Army, results have been most disappointing. It seems to the present writer that several factors have been overlooked. In the first place, and this is, perhaps, the most important of all, there is a natural prophylaxis in the normal healthy adult. Many a person in a fever stricken district may have parasites in the blood without having any other indication of the disease. But should such a person receive a severe injury, be unduly exposed to the sun, or catch a chill, an attack of fever is sure to follow. The reason is that the exciting cause has temporarily lowered the patient's resisting capacity, and the parasites have taken advantage /

advantage of the situation, increased their sporulating activities, and liberated their toxins, thus producing the clinical manifestations. In such a healthy adult even comparatively small prophylactic doses of Quinine e.g., three or four grains a day, would be sufficient to turn the scale in his favour, and would prevent the parasites from remaining in the system. It is far otherwise in those cases where the system has already been weakened, and the resisting powers lowered by repeated attacks of Malaria. Here Quinine has to fight as it were singlehanded, without the help of natural prophylaxis, and unless the doses are larger or given more frequently, the prophylaxis will not be complete.

Again, in the case of jails in India where some of the best results have been obtained, we find that good hygiene prevails, and high walls separate the inmates from their unhealthy surroundings. No opportunity is given for mosquitoes to breed anywhere near the jails, and hence only a stray infected mosquito finds its way in. The 'infective incidence' is very low, and the effects are easily antagonised by the usual dose of ten or fifteen grains twice a week. How different is the case of the ordinary villager! Living in an unhygienic neighbourhood, surrounded by pools teeming with larvae, and by patients and carriers ready to infect these as soon as they mature, what wonder is it that the same prophylactic dose should prove insufficient to protect him? In such a case the blood should be saturated with Quinine, and four /

four grains three times a day would not be too much to give him to ensure complete protection.

Take the case of soldiers encamped in, or marching through, a malarious district. Here the results have been most disappointing. But why? Is the cause of failure not to be sought for in the heavy 'incidence of infection' to which such soldiers are exposed, together with the fatigue of night marches, exposure to the sun by day, and the cold by night, which are incidental to such a life? A much larger dose than gr. IV. or V. per diem is necessary to ensure prophylaxis.

Finally there is the psychological attitude of the individual which must also be taken into account. In many cases the prophylactic dose, no doubt with the best of intentions, has been forced upon an individual unwilling to receive it, or sceptical of its powers. The result will not be the same as in the case of one who thoroughly believes in it, and is anxious to take it. Much more might be done by instruction and demonstration both in the Army and elsewhere to produce a suitable psychological attitude which would help considerably to make Quinine prophylaxis more effective.

As regards the most efficient prophylactic dose the findings of Prof. Wartz^{ss} in Macedonia shew that the best results were obtained by the daily administration of Quinine in fifteen grain doses. Some authorities have advocated a single dose of fifteen or twenty grains given twice a week. This method has /

has not been followed by the writer on account of the danger of impairment to hearing already mentioned when dealing with the question of dosage.

The writer's own experience has been somewhat limited, but it has tended to strengthen his faith in the administration of four grains of Quinine, or its equivalent of Cinchona Alkaloid, every night during the fever season with an additional four-grain dose if there has been undue fatigue, or exposure to chill or sun. The dose is given preferably at night partly because that is the time when infection is most likely to occur ; but chiefly because, if there is any tendency towards Cinchonism, the effects will pass off during sleep, and will not interfere with the work of the following day. We think it better to have Quinine continually in the circulation than to risk the absence of it for two or three days before the next large dose is given. This dose of four grains would be sufficient in ordinary healthy adults ; but where the individual is exposed to heavy infection, or is already in an enfeebled condition, the amount should be raised to eight grains at night, and an additional four grains given in the morning where this is insufficient. Larger doses than these need never be given as a prophylactic.

It will thus be seen that the prophylaxis of Malaria to be complete, must include measures taken to prevent infection, to ensure efficient treatment and to vary the prophylactic dose.

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